REMARKS/ARGUMENTS

Claims 119-123 are pending in this application and are rejected on various grounds. No claims have been amended in this submission.

Further, Applicants submit a copy of the Declaration of Audrey D. Goddard in this submission which supplements the arguments already presented in the response of June 13, 2005. This submission merely serves to complete the record concerning the value of gene amplification data in support of specific and substantial asserted utility, as explained below. Consideration of this declaration is respectfully requested. No new matter is added by way of this submission.

Applicants had previously submitted that the results of the TaqMan™ PCR, reported in ΔCt units, are disclosed in the passage on page 539, lines 37-39 of the instant specification. As explained therein, one unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on. Using this PCR-based assay, Applicants showed that the gene encoding for PRO1009 was significantly amplified, that is, it showed approximately 1.06-2.10 ΔCt units which corresponds to $2^{1.06}$ -$2^{2.10}$- fold amplification or **2.085 fold to 4.287-fold** amplification in colon tumors, and thus the PRO1009 gene has utility as a diagnostic marker of colon cancer.

In support of their showing that these gene amplification values are significant, Applicants submit herewith, a Declaration by Dr. Audrey D. Goddard. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy (Emphasis added).

Accordingly, the **2.085 fold to 4.287-fold** amplification for colon cancer would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

Further, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (submitted with Applicants' Response filed June 18, 2004) collectively teach that in general, gene amplification increases mRNA expression. Applicants further submitted that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede), a polypeptide encoded by an amplified gene in cancer would **still** have a specific, substantial, and credible utility as explained below. The Declaration of Dr. Avi Ashkenazi had supporting evidence for such a utility in a real-world example (the HER-2/ Neu example) presented in an article by Hanna and Mornin (both submitted with Applicants' Response filed June 18, 2004). The article supported the view that, even when the protein is not over-expressed, an assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Thus, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin, one skilled in the art would appreciate that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not over-expressed. This leads to better determination of a suitable therapy for the tumor. Thus, Applicants submit that the significant gene amplification data lends utility support for the PRO1009 protein and its antibodies as well.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney Docket No.: **39780-2730P1C12**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 4, 2005

By: _____ (43,626)
Daphne Reddy (Reg. No. 53,507

on behalf of Daphne Reddy

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